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A Comprehensive Review of the Evaluation of in Situ Gels

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Abstract:- In situ gels are now among the most widely used and widely available systems. These systems minimize drug administration frequency because of their special sol-to-gel transition properties, increasing patient comfort. Other benefits of these systems include easy production, improved adherence, and ease of use. 'Sol-gel' produces a colloidal suspension or solution by hydrolyzing the precursor and then polymerizing it through condensation. These in situ gelling techniques gel at the accomplishment site because they can be administered as solutions. Recently, several researchers developed liposomes, microspheres, nanoemulsions, nanospheres, and other in situ gelling systems. One of the greatest innovative drug delivery methods to date is the "in situ gel" system, which promotes better patient comfort and compliance as well as a prolonged and regulated release of the medication. With in situ gel formation, a variety of natural and synthetic polymers may find application in oral, ophthalmic, transdermal, buccal, intraperitoneal, parenteral, injectable, rectal, and vaginal routes. Research on the in-situ gel system has a lot of potential to offer cutting-edge methods for medication delivery systems.

Keywords:- *In Situ Gels, Sol-Gel, Polymers, Innovative Drug Delivery, Patient Comfort.*

I. INTRODUCTION

In situ, gelling is polymeric formulations that, although initially in sol form when ingested by the body, transform into gel forms when subjected to physiological circumstances. The sol-gel transition is triggered by various factors, including changes in pH, temperature, solvent exchange, UV radiation, and the presence of certain ions or molecules. Due to its many advantages, including its unique sol-to-gel transition feature that minimizes the frequency of drug administration and improves patient comfort and adherence, it has enormous potential as a delivery system. Moreover, it offers liposomes, nanospheres, microspheres, and in situ gelling nanoemulsions.[1, 2] Buccal, intraperitoneal, nasal, ophthalmic, oral, parenteral, rectal, subcutaneous, transdermal, and vaginal routes, have the potential to be employed in situ gels. In the discovery phase, the gel formulations improve the local and systemic exposure of possible lead compounds, making them perfect for rapidly and economically creating animal models for a range of disorders.[3] In situ gels can be created using a variety of biodegradable polymers, but there are several drawbacks, including challenging processability, burst effect, irreversible drug release kinetics, and the need for organic solvents during preparation (particularly in synthetic polymer-based systems). Natural polymers meet all of the requirements for the perfect polymer, but because they are difficult to repeat from batch to batch, synthetic polymers are utilized instead. The natural polymers employed for in situ-producing oral drug delivery systems are pectin, xyloglucan, and gellan gum. Natural polymers including gellan gum, alginic acid, and xyloglucan are the most often employed polymers for in situ gels-based ocular administration.[4]

II. REPORTED FORMULATIONS RESEARCH

Shailaja Pashikanti et al. (2019) reported the formulation and evaluation of a floating in situ gel of ciprofloxacin. Different amounts of calcium carbonate, a cross-linking agent, and sodium alginate, a biodegradable polymer that forms in situ gels, were used to create in situ gel formulations. The formulations were assessed for drug content, viscosity, in vitro floating behavior, pH, in vitro drug release, and in vitro gelling capability. FTIR analysis was done on the Ciprofloxacin, excipients, and formulation optimization. Every formulation exhibited the ideal viscosity for easy swallowing and administration. various formulations had a floating lag period of 32–70 seconds and floated for more than 12 hours. As the amounts of gelling agent and polymer increased, so did the in vitro gelling capability. Out of all the formulations, F4, which contained 4% w/v sodium alginate and 4% w/v calcium carbonate, demonstrated a sustained 95.6% in vitro drug release over 12 hours. No interactions between the medication and the excipients were found in the FTIR investigations. Drug release from the formulations was characterized by Fickian diffusion and First Order Kinetics.[5]

Vishwa K. et al. (2023) evaluated in situ gel eye drops containing nanoparticles of Gemifloxacin Mesylate. Using a 3^2 factorial design, the ionic gelation process was used to create the nanoparticles. To crosslink Chitosan, sodium tripolyphosphate (STPP) was utilized. With 0.15% Gemifloxacin mesylate, 0.15% chitosan, and 0.20% STPP, the optimized nanoparticle formulation (GF4) produced a particle size of 71 nm and an entrapment effectiveness of 81.11%. The synthesized nanoparticles exhibited biphasic release, releasing 15% of the drug in a burst in 1.0 hours and 90.53% cumulatively for 24 hours. Following that, an in-situ gel was created utilizing the produced nanoparticles and Poloxamer 407, resulting in a prolonged drug release with

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effective antibacterial activity against both gram-positive and gram-negative bacteria, as demonstrated by the cup plate method.[6]

Sakshi Nainwal et al. (2020) formulated and evaluated Ofloxacin eye gel which is used in the treatment of conjunctivitis. Sodium alginate was selected as the ophthalmic gel-forming gelling ingredient for the gel formulation. To achieve an appropriate consistency, hydroxypropyl methylcellulose was used as a viscosity booster. The initial assessments include variables like appearance, the gel drug's pH content, rheological investigations, spreadability, and extrudability. For every formulation, the in-situ gel solution's pH was found to be between 7.58 and 6.58. The pH of formulation F3, is utilized for ophthalmic treatments. Gelation occurs instantly in F3. The formulations' polymeric content directly influenced the viscosity. When HPMC is added, formulations become more viscous and exhibit higher pseudo-plasticity (F1–F3) in comparison to F4 which is made without HPMC. Among the produced formulations, F3 exhibits favorable outcomes due to its elevated concentration of sodium alginate and HPMC. Percentage drug release in the case of In-situ gel of ofloxacin was found to be 92.46% release in 7h.[7]

Dasharath M. Patel et al. (2011) reported a Floating Oral *In Situ* Gelling System of Amoxicillin. Sodium alginate, calcium chloride, sodium citrate, hydroxypropyl methylcellulose, and sodium bicarbonate were used to create formulations for floating in situ gelling. The in vitro drug release, total floating time, floating lag time, and solution viscosity of the produced formulations were assessed. A 3^2 complete factorial design was utilized to optimize the formulation. To determine the kinetics of drug release, dissolution data were fitted to different models. For the dependent variables, regression analysis and analysis of variance were carried out. Since batch F 8 drug release matched the theoretical release profile more closely (f_2 = 74.38), it was deemed to be the best. Thus, Sodium alginate can be used as a gelling polymer in an amoxicillin floating in situ gelling system to create a drug release that lasts for 10 to 12 hours with zero-order release kinetics.[8]

Thawatchai Phaechamud et al. (2022) reported the Design and Comparative Evaluation of Vancomycin HCl-Loaded Rosin-Based In Situ Forming Gel and Microparticles. To treat periodontal disease, vancomycin HCl was added to rosin in situ forming gel (ISG) and rosin in situ forming microparticles (ISM) to create a local drug delivery system. Measurements were made of the ISG and ISM's pH, viscosity, injectability, adhesion characteristics, in-vitro transformation, and drug release, among other physical attributes. Additionally, the agar-cup diffusion method was used to investigate the antibacterial activity's efficacy against *Escherichia coli, Porphyromonas gingivalis, Streptococcus mutans,* and *Staphylococcus aureus.* ISG and ISM based on rosin and loaded with vancomycin HCl showed ease of injection with an injection force of less than 20 N, and their pH values fell between 5.02 and 6.48. Furthermore, 40–60% rosin-based ISM demonstrated good emulsion stability, and the lubricity impact of the external oil phase of ISM encouraged less work of injection than ISG. Emulsions with 40%, 50%, and 60% rosin had droplet sizes of 98.48 ± 16.11, 125.55 ± 4.75, and 137.80 ± 16.8 µm, in that order. The resulting microparticles shrank as a result of solvent loss from solvent exchange, resulting in 78.63 ± 12.97, 93.81 ± 10.53, and 118.32 ± 15.61 µm diameter, respectively. Furthermore, the size of the microparticles grew as the rosin content rose. Following phase transformation, all formulations exhibited greater flexibility than elasticity, allowing them to readily conform to the unique geometry of a patient's gum cavity. With ISG, inhibitory zones were observed against *S. mutans* and *P. gingivalis* in both developed ISG and ISM. The rosin ISG and ISM loaded with vancomycin HCl exhibited effective antibacterial activity and a 7-day drug release delay; as such, they showed promise as drug delivery vehicles for the treatment of periodontitis.[9]

Dandagi et al. (2020) investigated the formulation and evaluation of oral floating in situ gel of cefixime trihydrate by using the β-cyclodextrin complexation technique for solubility enhancement. Sodium citrate was used as a complexing agent, calcium carbonate as a gas-generating agent, and gellan gum and sodium alginate as gelling agents to create in situ gel formulations. Every formulation displayed floating after 60 seconds and had a 20-hour floating duration overall. Formulation F2 is deemed optimal as it demonstrated the highest drug release, specifically 89.02%, by Huangchi's diffusion process. When the in-situ gelling systems come into contact with SGF, they immediately gel and continue to float. increased Cefixime Trihydrate's gastro-retentive time in the stomach. The drug content in the gel and solution was between 85 and 115%, which is an acceptable range and guaranteed dosage consistency in the formulation. For F2, the drug concentration was at its highest. All of the formulations' drug entrapment efficiencies were determined to be greater than 95%, indicating that no appreciable drug was lost during formulation and that the maximum amount of drug was released.[10]

Satyajit Sahoo et al. (2020) reported the formulation and evaluation of sustained release in-situ gel of amikacin by using 3^2 full factorial designs for ophthalmic delivery to overcome the problems of poor bioavailability. To create ion-sensitive and temperature-sensitive ophthalmic in-situ gel, poloxamer 407, a temperature-activated gelling agent, and gelrite, an ion-activated gelling agent, were combined. Several characteristics, including pH, appearance, drug content, viscosity, in-vitro release, sterility test, and stability studies, were assessed for the produced formulations. The concentration of gelrite and poloxamer 407 in this investigation determines the release profile. For ten hours, the chosen formulation demonstrated sustained release. As a result, it demonstrated longer residence and eye contact times. An improved formulation for the eye irritation test was used to conduct the Draize test. It was found that the rabbit eye was not irritated by it.[11]

Mohammed Elmowafy et al. (2021) investigated Mucoadhesive In Situ Rectal Gel Loaded with Rifampicin to Improve Bioavailability and Alleviate Liver Toxicity. In the beginning, a co-precipitate of RF/polyethylene glycol 6000

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was made in various ratios. Following an investigation for drug/polymer interaction based on drug solubility, the chosen ratio was included into in situ rectal gels utilizing Pluronic F127 (15%) and Pluronic F68 (10%) as a building block for gel and mucoadhesive polymers (chitosan, sodium alginate, and HPMC). The gel strength and gelation temperature of the formulations were evaluated. An investigation was conducted for in vivo evaluations of the chosen formulation. According to the findings, a drug/polymer ratio of 1:1 shown satisfactory solubility with the observed drug/polymer interaction. The addition of mucoadhesive polymers increased the gel strength and changed the gelation temperature to lower temperatures, depending on their concentrations. There was no noticeable rectal discomfort or anal leaking with the chosen formulation (F4). When compared to oral drug suspension and solid suppositories, F4 demonstrated greater drug absorption with a 3.38-fold and 1.74-fold higher bioavailability, respectively, using a validated chromatographic analytical method. Studies on toxicity revealed negligible liver damage based on biochemical, histological, and immunohistochemical analyses. When combined, F4 demonstrated the potential for improved performance and lesser liver toxicity, providing a promising treatment option.[12]

Ke Hu et al. (2021) reported Preparation and Characterization of Tacrolimus-Loaded SLNs in situ Gel for Ocular Drug Delivery for the Treatment of Immune Conjunctivitis. Surface shape, particle size, zeta potential, entrapment efficiency, drug loading, and in vitro release behavior were the characteristics of the ideal formulation. Additionally, in vivo investigations were carried out to assess the pharmacokinetic and pharmacodynamic consequences. In the current study, homogenization was used to create TAC-SLNs ISG, which were then subjected to the probe sonication procedure. TAC-SLNs ISG was found to have an average particle size of 122.3±4.3 nm. Particle size was not increased by in situ gel in comparison to TAC-SLNs, and no discernible difference was seen between the two. According to the results of the viscosity measurement, TAC SLNs-ISG were typical of pseudoplastic systems. They also demonstrated a noticeable rise in viscosity with increasing temperature, which finally resulted in the formation of a stiff gel at 32°C. Studies conducted in vivo and in vitro demonstrated the drug's sustained release model from TAC-SLNs ISG. Comparing TAC-SLNs ISG with eye drops and SLNs revealed that it had good pharmacodynamics in an animal model.[13]

Silvia Tampucci et al. (2021) investigated the Combination of Nano micellar Technology and In Situ Gelling Polymer as an Ocular Drug Delivery System (ODDS) for Cyclosporine-A. The nano micelles were created using two non-ionic surfactants: polyoxyl 40 hydrogenated castor oil, or RH-40, and d-α-tocopherol polyethylene glycol succinate, or VitE-TPGS. Using the CyA entrapment (EE%) and loading efficiency (LE%), cloud point (CP), regeneration time (RT), size, and polydispersity index (PI) measurements, we were able to determine the optimal surfactant mixture combination. This combination demonstrated appropriate stability, high CyA-EE (99.07%), very small and homogeneous dimensions, and favored the solubilization of an amount of CyA (0.144% w/w) similar to that found in commercially available emulsion Ikervis®. The optimized ion-sensitive polymeric dispersions of gellan gum (GG-LA: 0.10, 0.15, and 0.20% w/w) containing the chosen nanomicellar formulation that could initiate the sol-gel transition following instillation were examined from both biopharmaceutical and technological perspectives (osmolality, pH, gelling capacity, rheological behavior, wettability, TEM, and storage stability at 4 and 20 °C). By using this innovative combination method, we were able to improve the ocular bioavailability of CyA by creating transparent, easily infused aqueous dispersions that could gel viscosity when in contact with tear fluid. In addition, this novel ODDS demonstrated reduced cytotoxicity, inhibited CyA transcorneal penetration and extended the duration of CyA residence in the precorneal region in comparison to Ikervis®.[14]

Monowar Hussain (2021) reported Acyclovir in-situ gelling systems were prepared by using temperature-triggered polymer. The cold technique was used to develop the formulation. The various ratios of Pluronic F127 and HPMC E50 LV were created. As a preservative, benzalkonium chloride was used. Drug-polymer interaction, clarity, pH measurement, drug content (%), gelling capability, gelation temperature, viscosity, sterility, isotonicity, in-vitro drug release tests, ocular irritation, and short-term stability studies were among the criteria that were assessed for the formulations. The produced formulations were liquid at low temperatures, but when the Pluronic F-127 in the formulation comes into contact with the tear fluid, the solution changes into a very viscous gel at 37°C. Since the drug formulation drains from the cornea more slowly when it is viscous in the precorneal area, the medication's bioavailability will rise as a result. F6 was chosen for the developed formulation because of its 10-hour release and non-irritating, sterile, and stable qualities, which extend the drug's residence period and improve patient compliance.[15]

Roopa S. Pai et al. (2014) evaluated the design and optimization of novel in situ gel of mercaptopurine for sustained drug delivery. The best gelling polymer was determined by in vitro swelling investigations to be xanthan gum, and the tablets were made by direct compression. To enhance the drug's release from the tablet, sodium chloride was employed as a release modifier. The percentage of sodium chloride and xanthan gum was optimized using a 3^2 complete factorial design to achieve the required swelling index and release profile. Weight variation, hardness, friability, disintegration time, drug content, in vitro swelling experiments, and in vitro dissolving studies were all assessed for the tablets. In contrast to the usual tablet, which released the medication within 45 minutes, the optimally optimized formulation had a strong swelling index and extended the release up to 12 hours. The results of this study suggest that mercaptopurine-loaded in situ gel tablets may be useful in maintaining drug release throughout the gastrointestinal tract for an extended length of time, which may enhance oral bioavailability.[16]

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Maha Nasr et al. (2017) reported an Intranasally administered in situ gelling nanocomposite system of dimenhydrinate, characterization, and pharmacodynamic applicability in a chemotherapy-induced emesis model. PEG 400, labrasol, transcutol, and phospholipids were used to develop PEVs. Particle size, zeta potential, morphology, and entrapment efficiency (EE%) were assessed. A cisplatin-induced emesis model in rats was used to conduct pharmacodynamic testing of the nanocomposite in situ forming gel system. The system's sol-gel temperature, viscosity, and mucoadhesiveness were assessed, along with its food, water, kaolin intake, and stomach weight content. The chosen PEVs formula showed a surface charge of 0.83 mV, a particle size of 121 nm, and an EE% of 83% for DMH. The chosen nanocomposite in situ gelling formula revealed a mucoadhesive force of 0.62 N, a regulated release period of six hours, and a viscosity of 2.13 Pa.S. Thus, the reported nanocomposite system demonstrated efficacy in the intranasal administration of DMH, hence offering a potentially effective delivery method for analogous antiemetics.[17]

Madhugiri Prakash Venkatesh (2020) evaluated targeted drug delivery of methotrexate in situ gels for the treatment of rheumatoid arthritis. An investigation was conducted to see whether in situ gel of methotrexate sodium (MTS) could be a successful treatment for rheumatoid arthritis. It was created using polycarbophil (PCL) as a copolymer, hydroxypropyl methylcellulose K4M (HK4M), and pluronic F-127 (PLF-127) as the principal polymer. The Freund's Complete Adjuvant (FCA) model was used to evaluate effectiveness, while histopathology tests were used to determine biocompatibility. After 96 hours, the optimized in situ gel (M4) released 93.26 ± 2.39% MTS and exhibited thermoresponsiveness. Furthermore, MTS distribution was even in the syringeable and optimally sterile in situ gel. Wistar rats were used in in vivo investigations, showing a significant decrease in paw edema for the 28-day study period and biocompatibility with the injection site tissues.[18]

Ying Xie et al. (2020) investigated Doxorubicin-Loaded In Situ Gel Combined with Biocompatible Hydroxyethyl Cellulose Hemostatic Gauze for the Controlled Release of Drugs and Prevention of Breast Cancer Recurrence Post-surgery. The outcomes demonstrate that compared to commercially available oxidatively regenerated cellulose hemostasis gauze, HEC has a shorter metabolic duration, no peripheral nerve damage or allergy, and higher benefits. HEC is a physical hemostasis mechanism; it does not cause hemolysis or physiological hemostasis. Furthermore, the combination of HEC and GEL(DOX) successfully decreases tumor growth without causing cardiac toxicity or bone marrow suppression, in addition to effectively stopping bleeding. Following treatment, there is up to 90% tumor suppression, which extends the survival period to 58 days. In conclusion, because of its perfect biocompatibility, HEC hemostatic gauze has a wide range of clinical application possibilities. We believe that implanting HEC hemostatic gauze with GEL(DOX) at the surgical site following surgery will be a novel approach to prevent breast cancer.[19]

Kevin Garala et al. (2013) investigated the formulation and evaluation of periodontal in situ gel. Using various polymers, a temperature-sensitive in situ gel containing 0.1% w/v chlorhexidine hydrochloride was prepared by a cold method. A preliminary investigation was conducted to optimize several polymer kinds and concentrations, including Carbopol 934P, Gellan gum, Poloxamer 188, and Poloxamer 407. To optimize the impact of independent variables like Poloxamer 407 and Carbopol 934P on responses like gelation temperature, spreadability, cumulative percentage release at two hours, and time for 50% drug release (t50%), a central composite design was used. Clarity, pH, gelation temperature, spreadability, drug content, in vitro drug release, t_{50}%, and cumulative percentage drug release at two hours were assessed for each formulation. The assessment parameters' results showed that when each polymer's concentration rose, the drug release and gelation temperature both significantly decreased with an increase of t_{50}%. To determine the best factorial design formulation, the desirability function was applied. Formulation F6 was deemed to be the optimal formulation since it displayed the highest overall desirability of 0.6283. When the percentage relative error was computed, it became evident that the observed responses and the values predicted by the regression equations that were constructed were nearly in agreement. It was determined that all formulations' medication content, pH, and clarity were satisfactory. Additionally, every formulation demonstrated a continuous release of medication for six hours, effectively treating periodontal disease.[20]

Denitsa Momekova et al. (2022) reported the Formulation and Evaluation of Hybrid Niosomal In Situ Gel for Intravesical Co-Delivery of Curcumin and Gentamicin Sulfate. The thin film hydration method was used to develop a series of niosomes to assess the effects of concentrations of curcumin, cholesterol, and non-ionic surfactants. Due to the high entrapment efficiency values obtained for both drugs and the appropriate physicochemical parameters (morphology, size, PDI, and zeta potential), the formulation consisting of an equimolar ratio of Span 60, Tween 60, and 30 mol% cholesterol was chosen as the optimal composition. As a result, it was further incorporated into Poloxamers (407/188) and Poloxamers and chitosan-based in situ gels. The created hybrid systems exhibited appropriate rheological properties, gelling characteristics, and a sol to gel transition within the physiological range. Furthermore, the sustained release profile and delayed dissolution of both medicines (in contrast to niosomal suspension) are determined by the gel structure that forms at physiological temperatures. The formulations that exhibited the best phase transition temperatures of 31°C and 27 °C, the shortest gelation times of up to 35 s, and the typical rheological response of hard gels at body temperature were found to be those containing 20% w/w P407 and 8% w/w P188, with or without the addition of 10% chitosan solution. These formulations were chosen as the most appropriate for intravesical instillation. Curcumin and gentamicin can be delivered intravesically using the hybrid systems that have been presented, based on the proven synergistic antibacterial action of the active components, good sustained release patterns, and gel erosion kinetics.[21]

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Khaled M. Hosny et al. (2021) Investigated the development, optimization, in-vitro, and in-vivo assessment of nanocubosomal-based in situ gel loaded with natamycin for ocular fungal disease. Using phytantriol, PolyMulse, and Natamycin (NT) as the independent formulation components and particle size, entrapment efficiency, and inhibitory zone as responses, the NT-loaded cubosome (NT-Cub) formula was initially improved using an I-optimal design. Particle size and entrapment efficiency percentage were observed to increase with phytotantriol. While there was a decrease in particle size and EE%, there was a minor rise in the inhibitory zone with higher amounts of PolyMulse. The inhibition zone and entrapment efficiency percentage first increased with an increase in the NT level. Using 1.5% Carbopol 934, the improved NT-Cub formulation was transformed into an in situ gel system. The ideal mixture exhibited a pH-sensitive rise in viscosity, which favored extended retention in the eye. It became apparent that in simulated tear fluid, the in vitro release of NT was 71 ±4%. When compared to a commercial formulation and the NT suspension, the optimal formulation increased the NT's ex vivo permeation by 3.3 and 5.2 times, respectively. The ideal formulation of NT is less irritating than a commercial formulation, according to the in vivo ocular irritation test. This suggests that the developed formulation can lower the frequency of dosing required and cause less eye discomfort.[22]

Thawatchai Phaechamud et al. (2022) investigated Imatinib Mesylate-Loaded Rosin/Cinnamon Oil-Based In Situ Forming Gel against Colorectal Cancer Cells. Using the development of imatinib mesylate (IM)-loaded rosin/ cinnamon oil (CO)-based in situ forming gel (ISG), the impact of rosin with the addition of CO was evaluated on the physicochemical properties and in vitro drug release. Additionally, HCT-116 and HT-29 cell lines were subjected to in vitro cytotoxicity testing. Every formulation showed easier injectability and Newtonian flow behavior with a viscosity of less than 266.9 cP. The rosin gel that was produced had less hardness and more adhesive force once CO was added. When viewed under a microscope, the gel formation grew over time. Over 28 days, CO-added ISG increased the release of IM and exhibited a particle-like gel appearance. At various incubation durations, all evaluated ISG formulations were found to be cytotoxic against the HCT-116 and HT-29 cell lines.[23]

Hari Kumar et al. (2013) investigated the design and development of a sustained-release injectable in situ gel of cytarabine. To offer prolonged release of the medication, a pH-triggered or ion exchange in situ gelling system for cytarabine was developed. This system is based on polymeric carriers that undergo sol-to-gel transition in response to pH changes. The sodium alginate, which served as a viscosity-enhancing ingredient, and polyacryl acid (Carbopol 934 NF) were used to manufacture the cytarabine in situ gelling system. The created formulation is a good substitute for traditional injectables because it is stable, non-irritating, and offers steady release over 24 hours.[24]

S. S. Saurabh et al. (2023) reported formulation and evaluation of cetirizine hydrochloride pH trigged in-situ ocular gel. The pH-trigged approach was used to create the CTZ in-situ ocular gel. Using a one-viscosity building polymer (HPMC E4M) and a pH-sensitive gelling agent (Carbomer), an in-situ CTZ ocular gel was created. Every formulation was assessed for appearance, pH, gelling capability, viscosity at various pHs, percentage of drug content, and drug release. 3^2 factorial designs were used to successfully prepare and optimize nine formulations. Version 13.0.10.064 of the DoE program was used for optimization. Each of the nine in-situ ocular gel compositions was evaluated. Of the nine formulations, F3 required the least quantity of polymer and had a strong gelling capacity. The optimized formulation had a uniform and translucent appearance. The F3 formulation's pH of 5.55±0.07 is suitable for sustaining formulation during the solution stage. The F3 formulation's viscosity at 20 RPM and pH 5.5 is 837.30±1.00 cps; this range of viscosity has good flow characteristics. The F3 formulation's viscosity at 20 RPM and pH 7.4 is 6800.74±1.58 cps; this range of viscosity has an excellent gelling capability that aids in drug retention at the surface of the eyes. There is a 100.16±0.53% drug content. The drug release at 300 minutes is 69.22±2.12, suggesting that it may stay at the surface of the eye for longer than 300 minutes. This is beneficial for lowering the frequency of doses.[25]

Tadavi S. Amarsing et al. (2023) evaluated the Development of Nasal In-situ Gel Formulation of Fexofenadine HCl Using Gellan Gum (Gelerite®). Gelerite, HPMC K4M, and β-cyclodextrin formulations were utilized for the production of in situ nasal gel. Drugs, polymers, and physical combinations of drug polymers were all studied using FTIR. These studies showed that there haven't been any significant changes to the drug bands as compared to pure drugs. Therefore, there is no drug-polymer interaction in the formulation, according to the FTIR analysis. The viscosity of the formulation was measured using a Fungilab Brookfield viscometer to estimate rheological research. The rheological characteristics of the gel and solution were found to range from 2740 ± 1.55 to 4675 ± 1.43 and 91 ± 1.73 to 125 ± 0.77, respectively. It was determined that the gel strength of formulas F1 through F9 ranged from 34 ± 1.00 to 51.23 ± 1.77 seconds. It was demonstrated that the formulation's viscosity dropped as the shear force increased, displaying shear thinning behavior. As the polymer ratio increased, a rise in formulation viscosity was seen. An in-vitro diffusion analysis was performed on each formulation to show how different parameters affect the formulation's capacity to release the medicines.[26]

Rohan Chhabra et al. (2023) reported the formulation and evaluation of oral floating Rabeprazole in situ gel for Gastroesophageal reflux disease (GERD). The pre-formulation investigations comprised the following: characterization of the active ingredient (API), solubility, melting point, λ_{max} calculation, standard calibration curve, and drug and excipient compatibility study. For the formulation of Rabeprazole oral floating in-situ gel, an ion-activated technique was employed. Different formulations (F1-F9) have been produced with varying concentrations of polymers, such as HPMC K100M and sodium alginate. A variety of physicochemical characteristics, including

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viscosity, drug content, in-vitro drug release studies, appearance, clarity, and in-vitro gelling capability and gelling duration, were assessed for the formulations. Properties such as gel strength and viscosity increase as the concentration of polymers increases. Based on its optimal viscosity and strong gelling capacity, F4 was chosen as the best formulation. The percentage of drug content found was 97.6%. For 12 hours, F4 displayed 95.16% in vitro drug release. The chosen formulation best fits the Higuchi kinetic model and is based on first-order kinetics, which states that the rate of drug release depends on concentration. For 90 days, stability experiments were conducted for F4 formulations per ICH recommendations. The stability was confirmed, and no appreciable changes in physicochemical parameters were detected.[27]

Rençber et al. (2020) investigated the characterization of fusidic acid-loaded in situ gel formulations for ophthalmic application. Poloxamer 407 and sodium carboxymethyl cellulose were used in the cold approach to generate temperature-triggered in situ ocular gel formulations. The pH, clarity, gelation temperature, mechanical, rheological, and in vitro drug release of the in situ gels were assessed. The formulations containing fusidic acid gelled at temperatures ranging from 29 to 33°C. At 32 ± 0.1ºC, the in situ gel displayed non-Newtonian pseudoplastic flow, similar to a shear thinning system, resembling tear fluid. Studies on the breakdown of fusidic acid in vitro revealed that within 12 hours, at least 65% of it was liberated. This study's findings suggest that fusidic acid-loaded in situ gels could be a viable therapeutic option for bacterial conjunctivitis in the eyes.[28]

Patel et al. (2015) investigated the formulation and evaluation of clindamycin HCl in situ gel for vaginal application. These formulations include an in-situ gel system for vaginal administration based on gellan gum (an ion-activated gelling polymer) and hydroxypropyl methylcellulose (0.1%) loaded with clindamycin. In addition to stability investigations, the produced formulation was evaluated for several in vitro characteristics, including drug release profile, statistical release kinetics, bio-adhesive force, clarity, refractive index, pH, and viscosity. Model membranes made of cellophane moistened with a modified version of simulated vaginal fluid were utilized to mimic vaginal circumstances. It was determined that the created formulation had good retention qualities, was bio-adhesive, and was not irritating. The medication content of the formulations ranges from 98.1 to 101%, and their clarity and appearance are satisfactory. The gel's refractive index, which ranges from 1.335 to 1.337, attests to its transparency. Moreover, after two hours, the formulation showed 33.3% cumulative drug release. 98.9% after 12 hours and 67.4% after 6 hours. In summary, the developed formulation ought to be stable. Formulation is therefore a good substitute for traditional vaginal dose forms.[29]

Mohammed Gulzar Ahmed et al. (2021) reported the Preparation and evaluation of in-situ gels containing hydrocortisone for the treatment of aphthous ulcers. Temperature-induced in-situ gels were made with different methylcellulose concentrations. The produced formulations were assessed for drug content, in vitro and ex vivo tests, pH, viscosity, syringeability, spreadability, gelling capability, and sol-gel transition temperature or gelation temperature. The developed formulation gelation temperatures have been determined to be between 32-39ºC. The formulation pH was found to be 6.8, and their drug concentration ranged from 76.40 to 94.7%. For eight hours, in vitro drug release was conducted with phosphate buffer serving as the diffusion medium. A sustained release behavior was demonstrated by an in-situ gel formulation with 1% w/v methylcellulose as the gel base, which extended the drug release for up to 8 hours. These in-situ gel compositions allowed for first-order drug release kinetics. Eventually, it can be concluded that an in-situ gel formulation with 1% w/v methylcellulose promotes longer drug residence times and delayed drug releases, both of which increase the bioavailability of pharmaceuticals. After conducting the short-term stability studies, no notable alterations were found.[30]

Koshy M. Kymonil et al. (2020) investigated Nasal mucoadhesive thermoreversible in situ gel of phenytoin sodium for the treatment of epilepsy. The thermoreversible polymer Pluronic F127, polyethylene glycol 4000, and propylene glycol were used in the cold approach to make the in situ gel, which would increase nasal residence duration, drug absorption across the nasal-mucosal membrane, improve bioavailability, and reduce the dosage. The characteristics of the in situ gel were drug concentration, mucoadhesive strength, pH, viscosity, gelation temperature, gelation time, and % cumulative release. It turns out that the different gelation temperatures and times of formulations fell between 28-38 °C and 90 and 164 s, respectively. It turned out that the pH was between 5.9 and 6.8. It emerged that the mucoadhesive strength of several formulations ranged from 47.032 to 126.775 g. It came to light that the total percentage release of phenytoin sodium across various formulations ranged from 39.2 to 53.2%. In conclusion, the phenytoin sodium in situ gel that has been developed is a perfect substrate for treating particular types of epilepsy.[31]

Sonali A. Nagare et al. (2018) reported Development and Evaluation of Nasal Mucoadhesive in Situ Gel Formulations of Carbamazepine Using In Vitro, Ex-Vivo, and In-Vivo Methods. Based on solubility studies, a 0.5% (W/W) mucoadhesive in-situ gelling polymer (Deacetylated Gellan gum) prepared as a mucoadhesive in-situ gelling formulation of carbamazepine using the spontaneous emulsification method (titration method) with Capmul MCM as the oil, Tween-80 as the surfactant, and PEG-600 as the co-surfactant phase. The following formulations were assessed: stability, drug content, penetration through sheep nasal mucosa, histological examination of the mucosa, pharmacodynamics investigation in rats, gelation, viscosity, gel strength, mucoadhesion, and stability. The in-situ gelling mucoadhesive Carbamazepine formulation shows diffusion of 94.30 ±0.01% drug in 360 min, attributed to the existence of free drug entrapped in the in-situ mucoadhesive layer. In-vitro and ex-vivo permeation investigations demonstrated a first burst of drug release at 60 min. The formulation of carbamazepine for mucoadhesive in-situ gelling was effectively created by the spontaneous Mucoadhesive in-situ

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gelling mucoadhesive carbamazepine increased brain and plasma concentrations of the drug, according to in vivo pharmacokinetic experiments conducted in rats. A histopathological analysis revealed no evidence of nasal mucosal injury during penetration. When compared to the control, carbamazepine's anticonvulsant efficacy varied considerably by I.N. and I.V. It can be inferred that when compared to intravenous administration of an equivalent dose, nasal delivery of carbamazepine is more efficacious and has a quicker onset of action.[32]

Rathapon Asasutjarit et al. (2011) investigated the Optimization and evaluation of thermoresponsive diclofenac sodium ophthalmic in situ gels. The physicochemical parameters of Pluronic F127-based thermoresponsive diclofenac sodium ophthalmic in situ gels (DS in situ gel) were examined, including pH, flow ability, sol-gel transition temperature, gelling capacity, and rheological characteristics. The gels were made using a cold approach. The physicochemical characteristics of an improved formulation, both before and after autoclaving, as well as its potency for causing ocular irritation in SIRC cells and rabbits, were studied. It became clear that formulation compositions had an impact on the physicochemical characteristics of DS in situ gels. The products' sol-gel transition temperature reduced when Pluronic F127 content increased, while it tended to increase if Pluronic F68 concentration increased. In this investigation, carbopol 940 had an impact on the product transparency, pH, and gelling capability but did not affect the sol-gel transition temperature. The formulation that was optimized demonstrated a sol–gel transition with pseudoplastic flow characteristics at 32.6 ± 1.1 ◦C. The sodium content of the diclofenac was lost during autoclaving. Nonetheless, it was approved as safe for use in ophthalmology and may greatly raise the bioavailability of diclofenac sodium in aqueous humor. Finally, it was determined that the improved DS in situ gel might be used in place of the traditional diclofenac sodium eye drop. Nevertheless, autoclaving was ineffective for sterilizing this product.[33]

Balaji M et al. (2020) investigated the Preparation and evaluation of ibuprofen in-situ periodontal gel. The present investigation set out to create and assess an in situ gelling drug delivery system for ibuprofen employing dichloromethane and polycaprolactone. The surface pH, viscosity, syringeability, gelation temperature, gelling time, in vitro gelling capacity, drug content, and in vitro drug release of the developed in situ gels were assessed. The formulation F3, which had an 84% drug content and a gelation temperature of 36.33±0.57◦C, was chosen as the optimal formulation. After 96 hours, it revealed 95.45% in vitro drug release. The drug release mechanism uses the Higuchi model and adheres to first-order release kinetics. The chosen formulation had stability over three months.[34]

Diane J. Burgess et al. (2021) evaluated mucoadhesive *in situ* forming gel to deliver a novel drug molecule, Bupivacaine γ-linoleate (Bup-γL), for prolonged and more potent oral mucositis pain control. When the formulation comes into contact with the oral mucosa, it forms a mucoadhesive gel and is sprayable at room temperature. An adhesive protective barrier against irritating agents (food, bacteria, etc.) and Bup-γL anesthesia of the nerve cells would be used to treat the pain. Utilizing Pluronic® F127 and F68, in situ forming characteristics were attained. Noveon® or Carbopol® was used as a mucoadhesion booster. Techniques for preparing formulations were thoroughly examined. The gels' rheological characteristics, ex vivo mucoadhesion, gelation behavior, in vitro drug release, and sprayability were all described along with their physicochemical characteristics. It was found that the order in which the polymers are mixed significantly affected how long it took to prepare the blank formulations. Using the optimized procedure, a final drug content in the range of 6.21–6.51 mg/mL was produced. Hydrophobic Bup-γL was added, and this resulted in a considerable decrease in the gelation temperature. Carbopol® and Noveon® both markedly increased mucoadhesion without sacrificing the system's other key characteristics (drug content and gelation temperature). Because of the ionization of Bup-γL, the formulation's drug release exhibited pH-sensitive reactions, with lower pH favoring faster drug release. A viable method for controlling the pain associated with extended oral mucositis is presented in this study. Additionally, a viable framework for mucoadhesive in situ gels has been created that permits hydrophobic drug loading at a high level.[35]

Table 1 Summary of some of the Marketed Products of in Situ Systems[2]

Manufacturing Company	Name of the marketed product	Drugs used in the formulation
Akten	Akten TM	Lidocaine hydrochloride
Alcon Laboratories Inc.	Pilopine HS	Pilocarpine hydrochloride
Insite vision	Azasite	Azithromycin
Macromed	Cytoryn	Interleukin-2(IL-2)
Macromed	Regel Depot Technology	Human Growth Hormone
Merck and Co. Inc	Timoptic-XE	Timolol maleate
Spectrum Thea Pharmaceuticals	Virgan	Ganciclovir

III. CONCLUSION

The scientific community has become interested in gel-based systems as a novel medication delivery method throughout the last ten years. Hydrogels in solution form that go through gelation under different physiological conditions are called in-situ gels. Variations in temperature, pH, ion exposure, UV radiation, electrical sensitivity, and a crucial enzyme from which the medication is delivered continuously and under control are some of the variables that affect the gel's

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creation. With continuous drug usage and long-term drug availability, they are intended to detoxify the substance. Reduced administration frequency is one advantage of a controlled discharge pattern, which increases patient compliance. In comparison to traditional treatment, the drug's toxicity can be decreased by lowering its dosage. It is possible to get plasma drug availability through controlled drug delivery, which involves administering the medication for an extended period of time with zero order kinetics. The creation of novels with both natural and synthetic polymers has advanced significantly. These methods can employ a unique carrier to achieve extreme and considerably enhanced sustained medication delivery. These systems gel at the site of action because they can be administered as a solution. Ultimately, gels provide patient comfort and compliance in situ and are simple to use.

REFERENCES

[1]. Maryam Kouchak In Situ Gelling Systems for Drug Delivery Jundishapur J Nat Pharm Prod. 2014; 9(3): 20126.

[2]. Padmasri Budumuru, Ravouru Nagaraju, Damarasingu Prasanth A comprehensive review on in situ gels International Journal of Applied Pharmaceutics 2020;12(6):24-33

[3]. Mounika Konatham, Mounika Tejaswi Gorle, Naveen Pathakala, Vasudha Bakshi, Yaso Deepika Mamidisetti, Priyanka Chinthakindi, Rajendra Kumar Jadi In Situ Gel Polymers: A Review Int J App Pharm. 2021; 13 (1): 86-90

[4]. M. Madan, A. Bajaj, S. Lewis, N. Udupa, J. A. Baig In Situ Forming Polymeric Drug Delivery Systems Indian J Pharm Sci. 2009; 71(3): 242–251.

[5]. Shailaja Pashikanti, Jyothsna B Formulation and evaluation of floating in situ gel of ciprofloxacin Int J App Pharm. 2019; 11 (1): 198-204

[6]. Vishwa J. Kalaria, S. Saisivam, Anas Alshishani, Jameel S. Aljariri Alhesan, Sumit Chakraborty, Mohamed Rahamathulla Design and evaluation of in situ gel eye drops containing nanoparticles of Gemifloxacin Mesylate Drug Delivery 2023; 30 (1): 2185180

[7]. Deepika Joshi, Praveen Kumar, Sakshi Nainwal Ophthalmic formulation and evaluation of ofloxacin in- situ gel World Journal of Pharmacy and Pharmaceutical Sciences 2020; 9 (11): 1906-1918

[8]. Dasharath M. Patel, Divyesh K. Patel, Chhagan N. Patel Formulation and Evaluation of Floating Oral In Situ Gelling System of Amoxicillin ISRN Pharm. 2011; 2011: 276250.

[9]. Tiraniti Chuenbarn, Jitnapa Sirirak, Sarun Tuntarawongsa, Siriporn Okonogi, Thawatchai Phaechamud Design and Comparative Evaluation of Vancomycin HCl-Loaded Rosin-Based In Situ Forming Gel and Microparticles Gels. 2022; 8(4): 231.

[10]. Jinal Patel, Panchaxari Dandagi, Sujay Hulyalkar and Bapu Desai Formulation And Evaluation Of Oral Floating In Situ Gel Of Cefixime Trihydrate By Using β-Cyclodextrin Complexation Technique For Solubility Enhancement World Journal Of Pharmacy And Pharmaceutical Sciences 2020; 9 (10): 2613-2625

[11]. Satyajit Sahoo, Kirti Malviya, Nishant Oza, Anirud Solanki, Prasanta Kumar Mohapatra Formulation And Evaluation Of Sustained Release In-Situ Gel Of Amikacin By Using 3^2 Full Factorial Design IJPSR 2020; 11(7): 3333-3346.

[12]. Al-Joufi, F.; Elmowafy, M.; Alruwaili, N.K.; Alharbi, K.S.; Shalaby, K.; Alsharari, S.D.; Ali, H.M. Mucoadhesive In Situ Rectal Gel Loaded with Rifampicin: Strategy to Improve Bioavailability and Alleviate Liver Toxicity. Pharmaceutics 2021; 13: 336.

[13]. Kexin Sun,Ke Hu Preparation and Characterization of Tacrolimus-Loaded SLNs in situ Gel for Ocular Drug Delivery for the Treatment of Immune Conjunctivitis Drug Des Devel Ther. 2021; 15: 141–150.

[14]. Eleonora Terreni, Erica Zucchetti, Silvia Tampucci, Susi Burgalassi, Daniela Monti, Patrizia Chetoni Combination of Nanomicellar Technology and In Situ Gelling Polymer as Ocular Drug Delivery System (ODDS) for Cyclosporine-A Pharmaceutics. 2021; 13(2): 192.

[15]. Monowar Hussain Temperature triggered in-situ gelling system for ocular antiviral drug IJPSR 2021; 12(1): 281-291

[16]. Nagendra R., Roopa S. Pai, Gurinder Singh Design and optimization of novel in situ gel of mercaptopurine for sustained drug delivery Brazilian Journal of Pharmaceutical Sciences 2014; 50 (1): 107-119

[17]. Sara S. Barakat, Maha Nasr, Rania F. Ahmed, Sabry S. Badawy, Samar Mansour Intranasally administered in situ gelling nanocomposite system of dimenhydrinate: preparation, characterization and pharmacodynamic applicability in chemotherapy-induced emesis model Scientific Reports 2017; 7: 9910

[18]. Madhugiri Prakash Venkatesh, Tegginmat Pramod Kumar, Deeksha Ramananda Pai Targeted drug delivery of Methotrexate in situ gels for the treatment of Rheumatoid Arthritis Saudi Pharmaceutical Journal 2020; 28 (12): 1548-1557

[19]. Bai-Yi Yan, Bai-Lu Liu, Ling-Yu Yi, Gui-Ling Wang, Bai-Zhong Xue, Ying Xie Doxorubicin-Loaded In Situ Gel Combined with Biocompatible Hydroxyethyl Cellulose Hemostatic Gauze for Controlled Release of Drugs and Prevention of Breast Cancer Recurrence Post-surgery Biomaterials Science & Engineering 2020; 6(10):5959-5968

[20]. Kevin Garala, Parth Joshi, Malay Shah, A Ramkishan, Jaydeep Patel Formulation and evaluation of periodontal in situ gel International Journal of Pharmaceutical Investigation | 2013; 3 (1): 29-41

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT1075

[21]. Viliana Gugleva, Victoria Michailova, Rositsa Mihaylova, Georgi Momekov, Maya Margaritova Zaharieva, Hristo Najdenski, Petar Petrov, Stanislav Rangelov, Aleksander Forys, Barbara Trzebicka, Denitsa Momekova Formulation and Evaluation of Hybrid Niosomal In Situ Gel for Intravesical Co-Delivery of Curcumin and Gentamicin Sulfate Pharmaceutics. 2022; 14(4): 747.

[22]. Khaled M. Hosny, Waleed Y. Rizg, Hala M. Alkhalidi, Walaa A. Abualsunun, Rana B. Bakhaidar, Alshaimaa M. Almehmady, Adel F. Alghaith, Sultan Alshehri, Amani M. El Sisi Nanocubosomal based in situ gel loaded with natamycin for ocular fungal diseases: development, optimization, in-vitro, and in-vivo assessment Drug Delivery 2021; 28 (1): 1836–1848

[23]. Ei Mon Khaing, Torsak Intaraphairot, Jongjan Mahadlek, Siriporn Okonogi, Wiwat Pichayakorn, Thawatchai Phaechamud Imatinib Mesylate-Loaded Rosin/Cinnamon Oil-Based In Situ Forming Gel against Colorectal Cancer Cells Gels. 2022; 8(9): 526.

[24]. Kulwant Singh, Harpreet Kaur, S. L. Hari Kumar Design and development of sustained release injectable in situ gel of cytarabine Pharmacophore 2013; 4 (6): 252-267

[25]. Surendra Singh Saurabh, Kamal Singh Rathore, Santanu Ghosh Formulation and evaluation of cetirizine hydrochloride pH trigged in-situ ocular gel Int J App Pharm. 2023;15 (2):106-116

[26]. Tadavi SA, Pawar SP. Development of Nasal In-situ Gel Formulation of Fexofenadine HCl Using Gellan Gum (Gelerite®). International Journal of Pharmaceutical Quality Assurance. 2023;14(1):1-3.

[27]. Rohan Chhabra, K. Mahalingan, A Geethalakshmi, Pynskhemlin Syiemlieh Formulation and Evaluation of Rabeprazole Oral Floating In-Situ Gel Archives of Pharmaceutical Sciences and Research 2023; 13 (1): 122-131

[28]. Rençber S, Özcan Bülbül E, Üstündağ Okur N, Ay Şenyiğit Z. Preparation and detailed characterization of fusidic acid loaded in situ gel formulations for ophthalmic application. J Res Pharm. 2021; 25(1): 1-12.

[29]. Patel P, Patel P. Formulation and evaluation of clindamycin HCl in situ gel for vaginal application. Int J Pharma Investig 2015; 5: 50-6.

[30]. Sanjana A, Mohammed Gulzar Ahmed, Jaswanth Gowda BH Preparation and evaluation of in-situ gels containing hydrocortisone for the treatment of aphthous ulcer Journal of Oral Biology and Craniofacial Research 2021;11: 269–276

[31]. Gyan Mohan, Sandeep K. Singh, Mary Koshy, Pooja Chawla, Koshy M. Kymonil Nasal mucoadhesive thermoreversible in situ gel of phenytoin sodium for epilepsy Pharmaspire 2020;12 (3): 96-99

[32]. Sonali A. Nagare, Jeevan R. Rajguru, Vikas G. Rajurkar, and Mrunal K. Shirsat Development and Evaluation of Nasal Mucoadhesive in Situ Gel Formulations of Carbamazepine Using In Vitro, Ex-Vivo and In-Vivo Methods International Research Journal of Pharmacy and Medical Sciences 2018;1 (6): 69-75

[33]. Rathapon Asasutjarit, Suthira Thanasanchokpibull, Asira Fuongfuchat, Sukitaya Veeranondha Optimization and evaluation of thermoresponsive diclofenac sodium ophthalmic in situ gels International Journal of Pharmaceutics 2011; 411:128–135

[34]. Balaji Maddiboyina, Arthapu Hari Krishna, Makkena Ramya Sri, Pasupuleti Bhuvana Kalyani, Shaik Jabeena, Shaik Sharmila, Vankudavatu Lakshmibai Preparation and evaluation of ibuprofen in-situ periodontal gel Int. J. of Allied Med. Sci. and Clin. Research 2020; 8(1): 67-75

[35]. Tingting Li, Quanying Bao, Jie Shen, Rajesh V. Lalla, Diane J. Burgess Mucoadhesive in situ forming gel for oral mucositis pain control International Journal of Pharmaceutics 2020; 580: 119238